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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/730,751	12/08/2003	Stavros C. Manolagas	3650.1003-007	4492

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EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/730,751	MANOLAGAS ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15,16,18-21 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15,16,18-21,24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims:

The amendment received 30 October 2006 in response to the Office Action of 1 August 2006 has been entered. Claims 22 and 23 have been cancelled. Claims 13, 15-16 and 18-21 and 24 are pending in the instant application. Claims 16 and 24 have been amended and the amendment made of Record. The Katz Declaration submitted under 37 CFR § 1.132 has been received and made of record.

The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

Objections/Rejections Withdrawn

The objection to the priority citation to Application No. 09/413,958 in the specification is withdrawn in view of Applicants' amendment to the first paragraph of the specification to update the priority data.

All rejections to Claims 22 and 23 have been withdrawn. Applicants have cancelled the claims rendering all rejections moot.

The rejection of Claims 13, 15, 16, 18, 20, 21, and 24 under 35 U.S.C. 102(a) as being anticipated by Weinstein et al. (1998, J. Clin. Invest. 102:274-282) is withdrawn. The Katz Declaration filed on 30 October 2006 under 37 CFR 1.131 is sufficient to overcome the Weinstein et al. reference.

The rejection of Claim 19 under 35 U.S.C. 103(a) as being unpatentable over Weinstein et al. as applied to claims 13, 15, 16, and 18 in view of Jilka et al. and further in view of Kato et al. is withdrawn. The Katz Declaration filed on 30 October 2006 under 37 CFR 1.131 is sufficient to overcome the Weinstein et al. reference. Jilka et al. and Kato et al. do not teach or suggest all elements of the rejected claim in the absence of Weinstein et al. as the primary reference.

New/Maintained Grounds for Rejection

35 U.S.C. § 112, Second Paragraph

Claims 13, 15, 16, 18-21 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 recites incomplete method steps. Claim 13 is directed to a method of screening for "glucocorticoid analogs" but the method steps as recited are insufficient to accomplish the goal stated in the preamble. The claim recites contacting "cells with .....a test compound. It is unclear if the test compound is a known glucocorticoid analog, is being screened to identify it as a possible glucocorticoid analog, or is a test compound which is unrelated to glucocorticoid.

Claims 15 and 19-21 are rejected as dependent from a rejected claim.

Claim 16 is vague and indefinite for omitting essential steps. Claim 16 is an *in vivo* method for screening for compounds that increase bone mineral density. It is unclear how the sample required for step (b), the step of comparing the number of cells undergoing apoptosis following treatment with glucocorticoid to the number of cells undergoing apoptosis with a test compound, is to be obtained.

Claims 18 and 24 are rejected as dependent from a rejected claim.

35 U.S.C. § 112, First Paragraph:

Claims 13, 15, amended claim 16, 18-21 and 24 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of screening for compounds that cause less bone destruction (as measured by apoptosis) than do glucocorticoids *in vitro,* or *in vivo* in a murine animal model; or

an *in vivo* method of screening for compounds that increase bone mineral density in patients with glucocorticoid-induced osteoporosis utilizing a murine animal model

does not reasonably provide enablement for

an *in vitro* method of screening for compounds that stimulate bone development; or

an *in vivo* method of screening for compounds that stimulate bone development in a mammal other than a murine animal model; or

an *in vivo* method of screening for compounds that increase mineral density in patients with osteoporosis other than glucocorticoid-induced osteoporosis in a mammal other than a murine animal model

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention: the invention relates to *in vitro* and *in vivo* models for screening compounds to ameliorate glucocorticoid-induced bone destruction [paragraph 003 in USPGPUB 20040248078, the PGPUB of the instant application].

The claims are broadly drawn to a method of screening for glucocorticoid analogues that stimulate bone development and a method of screening for compounds that increase mineral bone density. The screening methods recite comparing the number of osteoblast and osteocyte cells undergoing apoptosis following treatment with glucocorticoid to the number of osteoblast and osteocyte cells undergoing apoptosis following treatment with the test compound. Thus, the claims recite a method of

screening for a test compound that causes less apoptosis, and presumably, less damage to the bone than that caused by glucocorticoids.

The specification discloses: A cardinal feature of glucocorticoid-induced osteoporosis is decreased bone formation [paragraph 006]. Glucocorticoid-induced bone disease, particularly glucocorticoid-induced osteoporosis in patients and in murine model, is accompanied by decreases in bone mineral density accompanied by increase in apoptosis of mature osteoblasts and osteocytes [paragraph 008]. The disclosure also teaches that treatment of mice with prednisolone resulted in decreased bone mineral density. Correlated with this decrease in bone mineral density is an increase in osteoblast and osteocyte apoptosis. As in mice, an increase in osteoblast and osteocyte apoptosis was documented in patients with glucocorticoid-induced osteoporosis [paragraph 0022]. However, the specification is silent as to whether increased apoptosis is a hallmark of osteoporosis of other etiologies, or whether glucocorticoid-induced osteoporosis is predictive of the pathology of other forms of osteoporosis. The specification envisions screening for compounds to prevent or ameliorate glucocorticoid- induced bone degeneration. It does not address screening for compounds which stimulate bone development in normal patients or in patients suffering from bone disease not caused by glucocorticoids. The specification fails to show a nexus between apoptotic osteoblasts and osteocytes in bone of patients suffering from osteoporosis other than glucocorticoid-induced osteoporosis and decreases in bone density

The working examples: Bone mineral density was measured in mice treated with placebo or prednisolone. The mice were sacrificed, and bone marrow aspirates were obtained for *ex vivo* marrow cell cultures. [Example 2]. Measurement of effects of glucorticoid administration on apoptosis in mice was done by TUNEL on samples obtained from sacrificed animals [Examples 7 and 12]. Increased apoptosis was also observed in bone biopsies taken from two patients treated with glucocorticoids, compared to bone from control patients [Example 13]. Thus, the working examples all disclose increases in apoptotic cells after treatment with glucocorticoids; the increase in apoptosis was detected in specimens obtained from sacrificed animals or by bone

biopsies. There are no other disclosures of obtaining samples *in vivo* for measurement of apoptosis.

The art recognizes that there are numerous causes of osteoporosis and that glucocorticoid- induced osteoporosis is but one of them. Thus, one could not predict that a compound identified by the methods of the instant invention would be able to stimulate bone development or increase mineral density in normal bone, or in patients suffering from any other form of bone disease or osteoporosis.

Applicants' claims are excessively broad due, in part, to the complex and diverse nature of bone formation and the numerous causative factors associated with osteoporotic disease. In addition, applicants are not enabled for screening for compounds in any *in vivo* other than the mouse model disclosed in the specification of the instant invention. The only disclosed method of obtaining a sample for determination of apoptotic cells is that of bone biopsy. This method would be excessively invasive for use as a step in a screening method in any other system than a laboratory animal model.

Therefore, due to the large quantity of experimentation required to determine a nexus between decrease in apoptosis of osteoblast and osteocyte cells *in vivo* in tissue from normal individuals or individuals suffering from bone pathologies other than glucocorticoid-induced osteoporosis, or a decrease in apoptosis of osteoblasts and osteocytes *in vitro* and an increase in bone development or bone mineral density, the lack of direction/guidance and the absence of working examples directed in the specification as to minimally invasive methods of obtaining samples to detect changes in apoptosis and the absence of working examples directed to correlation between changes in apoptosis in an *in vitro* model and bone development, the complex nature of the invention, the state of the art that teaches that there are many causes of osteoporosis, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention commensurate with the scope of the claims.

Conclusion

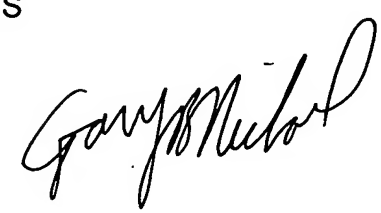
Due to the new grounds of rejection herein, this action is made non final. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SHS



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